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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,865	10/15/2001	J Kevin Donahue	56495-2 (71699)	3724

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EXAMINER	
KATCHEVES, KONSTANTINA T	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,865	DONAHUE ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,27,28,36-38,48-50,57-59,63,64,66 and 70-111* is/are pending in the application.

4a) Of the above claim(s) *27,28,36-38,48-50,57-59,63,64 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,70-83,85-91,93-99,102-105 and 108-111* is/are rejected.

7)☒ Claim(s) *84,92,100,101,106 and 107* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1,27,28,36-38,48-50,57-59,63,64,66 and 70-111 are pending in the present application. Claims 27,28,36-38,48-50,57-59,63,64 and 66 are withdrawn from consideration. Claims 70-111 are currently under examination. Upon review of Applicant's amendment and response and the text of the pending claims, it appears that further clarification of the prior office action is required and this non-final rejection is appropriate.

Response to Amendment

The rejection of claims 1, 70, 74 and 96 under 35 U.S.C. 102(b) as being anticipated by Goldring et al. (US Patent No. 5,516,651) has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 70, 74 and 96 under 35 U.S.C. 102(e) as being anticipated by Linden et al. (Pub. No. US 2002/0082240) has been withdrawn in view of Applicant's amendment.

The rejection of claims 1, 70, 71, 72 and 96 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of Applicant's amendment and arguments.

The rejection of claims 1 and 70-96 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sildenafil, zaprinast and T-1032, does not reasonably provide enablement for any PDE inhibitor or any bicyclic heterocyclic compound or any compound having the core structure pyrazolo[4, 3-d]pyrimidin-7-one, pyrazolo[3,4-d]pyrimidin-4-one, quinazolin-4-one, purin-6-one, or pyrido[3,2-

d]pyrimidin-4-one has been withdrawn in view of Applicant's amendment and arguments.

The rejection of claims 75 and 96 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of Applicant's amendment and arguments.

Claims 1,70-83, 85-91, 93-99, 102-106, and 108-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *ex vivo* methods of nucleic acid delivery and direct injection of nucleic acids, does not reasonably provide enablement for all *in vivo* methods of delivery.

Response to Arguments

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 70-83, 84, 86-89, 91 and 93-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *ex vivo* methods of nucleic acid delivery and direct injection of nucleic acids, does not reasonably provide enablement for all *in vivo* methods of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. The relevant factors have been set forth in the prior Office Action.

The nature of the invention and breadth of the claims and Response to Applicant's Arguments

Methods of targeting nucleic acids into host cells *in vivo* fall into the broad area of gene therapy. Successful gene therapy methods are based, fundamentally, upon the ability to deliver exogenous nucleic acids to cells or tissues of interest. The invention of the instant claims is generally drawn to a method of gene therapy and is broadly drawn to a method of administering nucleic acids to the cells of tissues *in vivo* by administering the nucleic acid with a cGMP-specific PDE-5 inhibitor.

By way of clarification, Applicant's amendment incorporating the language that the exogenous nucleic acid "to the tissue, wherein the tissue is a solid cell mass selected from the group consisting of a solid organ and a solid tumor," does not overcome the scope of enablement rejection previously set forth and repeated below. Applicant's arguments indicated that language of claim 85, which was not rejected previously rejected has been incorporated and thus the present claims are no longer subject to the present rejection. Upon further consideration of the amended language of claim 1 and the language of claim 85, the examiner interpreted the claim as being limited to "direct injection." This scope was indicated as enabled in the prior Office Action. However, the language of claim 1 and claim 85, given its broadest reasonable interpretation, does not recite a route of administration. The claims read on any route of administration so long

as the nucleic acid is delivered "to the tissue" or to the solid tumor or solid organ. How the nucleic acid reaches the tissue is not specified. Thus, Applicant is not enable for this entire scope for the reasons already of record and repeated below.

The state of the art, skill of those in the art and predictability of the art

Despite experimentation a tremendous amount of effort by skilled artisans in the field of gene delivery and expression *in vivo*, there remain significant hurdles known in the art to make and use the invention over the scope claimed. Anderson (Nature Vol. 392, supp 1998) reports that progress in developing effective gene therapy is slow. Anderson further states, "the efficiency of gene transfer and expression inhuman patients is, however, still disappointingly low. . . . [the] goal is more diffuclt to achieve than many investigators had predicted. . . [the] human body has spent many thousands of years learning to protect itself. . ." See page 25, column 1.

Verma et al. (Nature Vol. 389 1997), and Palu et al. (J. of Biotech. Vol.68 1999) also discuss the inherent difficulties transfecting cells *in vivo* by targeted delivery mechanisms. Transferred genes can be induced to function in a whole animal; however, no approach has been fully successful for *in vivo* gene transfer. See Verma page 239. Moreover, the main obstacle to the development of gene therapy is the targeted long-term expression of the transgene. The *in vivo* transfection of cells has not been fully successful for many reasons including the complexity the biological systems of living organisms, the inability of the genes to reach enough of the target cells, and the inability of the genes to function properly or for a significant period of time even if they do reach the cells. See Palu page 10 and Anderson page 25.

The quantity of experimentation necessary, the amount of direction or guidance provided, and the presence of absence of working examples

Applicant has not provided any working examples in the specification toward a method of administering nucleic acids to cells in a tissue of interest *in vivo*. Applicant only teaches that sildenafil, zaprinast or T-1032 pretreatment of myocardial tissue *ex vivo* before VEGF exposure shows an increase in transfection efficiency of exogenous nucleic acids in the cells increased in comparison to VEGF alone. These data, however, do not teach one of skill in the art how to direct the nucleic acid vector to its target location, deliver the nucleic acid to the target cell in a sufficient amount, or express the desired protein encoded by the nucleic acid properly.

In view of the factors above, the art of gene therapy and the art of gene delivery and expression is in its infancy and highly unpredictable. Therefore, the invention is not enabled for the full scope claimed by Applicant.

Allowable Subject Matter

Claims 84, 92, 100, 101, 106, 107 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571)

272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
Examiner
Art Unit 1636